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ORIGINAL ARTICLE

Increased Pulse Wave Velocity and Carotid Intima-Media Thickness in Patients with Ulcerative Colitis

Remzi Adnan Akdoğan · Murtaza Emre Durakoğlugil · Sinan Altan Kocaman · Yüksel Çiçek · Tuğba Durakoğlugil · Elif Ergül · Halil Rakıcı

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Abstract
Background Ulcerative colitis (UC) is characterized with chronic, progressive inflammation of the gastrointestinal tract. The association of UC with cardiovascular disease is still a matter of debate.
Aim The aim of this study was to investigate whether carotid intima-media thickness (CIMT) and carotid-femoral pulse wave velocity (cf-PWV) as surrogates of atherosclerosis and arterial stiffness are increased in patients with UC.
Methods Our study was cross-sectional and observational in design. Baseline characteristics were recorded during interview with the patient. Patients with previous cardiovascular disease, rheumatoid arthritis, chronic renal failure, and infectious and inflammatory disorders other than UC were excluded. Thirty-seven consecutive patients with UC and 30 control participants underwent cf-PWV assessment and CIMT measurement. The diagnosis of UC was based on clinical, radiologic, endoscopic, and histological findings.
Results CIMT, cf-PWV, and C reactive protein were significantly higher in patients with UC. Although linear regression analyses identified UC as an independent predictor of CIMT ($\beta \pm$ SE, 0.39 ± 0.08; $p < 0.001$), only age independently predicted cf-PWV ($\beta \pm$ SE, 0.08 ± 0.03; $p = 0.003$) in our study population. Moreover, we revealed higher CIMT and PWV values in patients with higher disease activity and more extensive involvement, compared to patients with mild activity and limited disease.
Conclusion We revealed increased pulse wave velocity and CIMT in patients with UC. UC appears to be associated with arterial stiffness and atherosclerotic burden, but the underlying mechanisms require further studies to be identified.

Keywords Atherosclerosis · Arterial stiffness · Carotid intima-media thickness · Pulse wave velocity · Ulcerative colitis

R. A. Akdoğan
Department of Gastroenterology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey

M. E. Durakoğlugil (✉) · Y. Çiçek
Department of Cardiology, Faculty of Medicine, Recep Tayyip Erdoğan University, Islampasa Mah., 53100 Rize, Turkey
e-mail: emredur@hotmail.com

S. A. Kocaman · E. Ergül
Department of Cardiology, Rize Education and Research Hospital, Rize, Turkey

T. Durakoğlugil
Department of Radiology, Faculty of Medicine, Recep Tayyip Erdoğan University, Rize, Turkey

H. Rakıcı
Department of Gastroenterology, Rize Education and Research Hospital, Rize, Turkey

Introduction

Ulcerative colitis (UC) is a form of inflammatory bowel diseases (IBD) characterized with chronic, progressive inflammation of the gastrointestinal tract. Since inflammation is closely related to atherosclerosis and low-grade chronic inflammation, as depicted by increased C reactive protein (CRP), predicts cardiovascular events [1]; there has been considerable interest regarding the association of atherosclerosis and inflammatory disorders. A significant relationship between atherosclerosis and systemic

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inflammatory disorders such as systemic lupus erythematosus and rheumatoid arthritis has been demonstrated [2, 3].

Arterial stiffness (AS) due to decreased arterial compliance is one of the major signs of vascular aging [4]. Several studies have documented the prognostic importance of arterial stiffness as an independent predictor of all-cause mortality and cardiovascular mortality [5, 6]. Carotid-femoral pulse wave velocity (cf-PWV) has been accepted as the gold standard measurement of arterial stiffness. Carotid-femoral pulse wave velocity is a well-recognized predictor of an adverse cardiovascular outcome with higher predictive value than classical cardiovascular risk factors and requires little technical expertise [7].

Non-invasive measurement of carotid intima-media thickness (CIMT) using B-Mode ultrasonography is a valid surrogate marker of atherosclerotic disease [8]. An increase in CIMT is associated with increased cardiovascular risk factors [9] and cardiovascular events [10]. CIMT is a reliable, reproducible and quantifiable method for detecting subclinical cardiovascular disease, which is independent of traditional risk factors [11].

Several studies have investigated the relationship between cardiovascular disease and inflammatory bowel diseases so far. Studies investigating the impact of IBD on CIMT have led to contradictory results [12–14]. Moreover, the association of arterial stiffness and UC has not been clarified till now. The aim of this study was to investigate whether CIMT and PWV as surrogates of atherosclerosis and arterial stiffness are increased in patients with UC.

Methods

Patient Selection and Study Protocol

Our study was cross-sectional and observational, consisting of 37 patients with UC (mean age, 48 ± 15 years) and 30 control participants (mean age, 45 ± 8 years). Thirty-seven patients diagnosed as having UC through clinical, radiologic, endoscopic, and histological findings were enrolled consecutively. Patient characteristics and medical history of patients including disease activity and medications were noted. Severity of UC was determined by Truelove and Witts classification [15].

Patients with previous cardiovascular disease, rheumatoid arthritis, chronic renal failure, and infectious and inflammatory disorders other than UC were excluded. Informed consent was obtained from all patients prior to the study. The study was performed in accordance with the principles stated in the Declaration of Helsinki and was approved by the Local Ethics Committee.

Control subjects were recruited from healthy volunteers without a history of either cardiovascular disease or IBD, who were seen by their family physician for routine annual examination and agreed to join a vascular health-screening study for research purposes.

Baseline characteristics were recorded during interview with the patient. Hypertension was defined as active use of antihypertensive drugs or documentation of blood pressure more than 140/90 mmHg. Diabetes mellitus was defined as fasting plasma glucose levels over 126 mg/dl or glucose level over 200 mg/dl at any measurement or active use of antidiabetic treatment. Patients who were using tobacco products on admission to our hospital and those who had quit smoking within the last year were considered as smokers. Body mass index (BMI) was calculated by the following formula: BMI = weight (kg)/height^2 (m).

Assessment of Pulse Wave Velocity

Carotid-femoral pulse wave velocity was measured as an index of arterial stiffness. Vascular assessments in both patients and controls were performed by a single experienced cardiologist who was blinded to patient data; the assessments occurred in the morning after an overnight fast and after refraining from cigarette smoking for the prior 8 h. PWV was calculated from the measurements of pulse transmission time and the distance between the two recording sites by a validated non-invasive device (SphygmoCor, AtCor Medical, Sydney, Australia). Carotid and femoral pulses were palpated to confirm measurement localization in the corresponding regions. Straight distances from the strongest point of pulses in the carotid and femoral area to the sternal notch were measured. The distance traveled by the pulse wave over the surface of the body was measured with a tape measure (from the sternal notch to right femoral artery minus the distance from the sternal notch to the right carotid artery) and was divided by the transit time; the result was expressed as meters/second (m/s) (Fig. 1). Resting blood pressure was detected by auscultation using a sphygmomanometer.

Measurement of Carotid Intima-Media Thickness

Ultrasonography was performed on all patients using a high-resolution ultrasonography scanner (Xario, Toshiba Medical Systems, Tokyo, Japan) with a PLT-805AT linear array transducer. Measurements were performed on the right and left carotid arteries. The patient was lying supine with the head directed away from the side of interest and the neck slightly extended. The transducer was manipulated so that the near and far walls of the CCA were parallel, and the lumen diameter was maximized in the longitudinal plane. The region 1 cm proximal to the carotid bifurcation was identified, and the CIMT of the far wall was evaluated as the distance between the lumen–intima interface and the media–adventitia interface. The CIMT was measured on the frozen

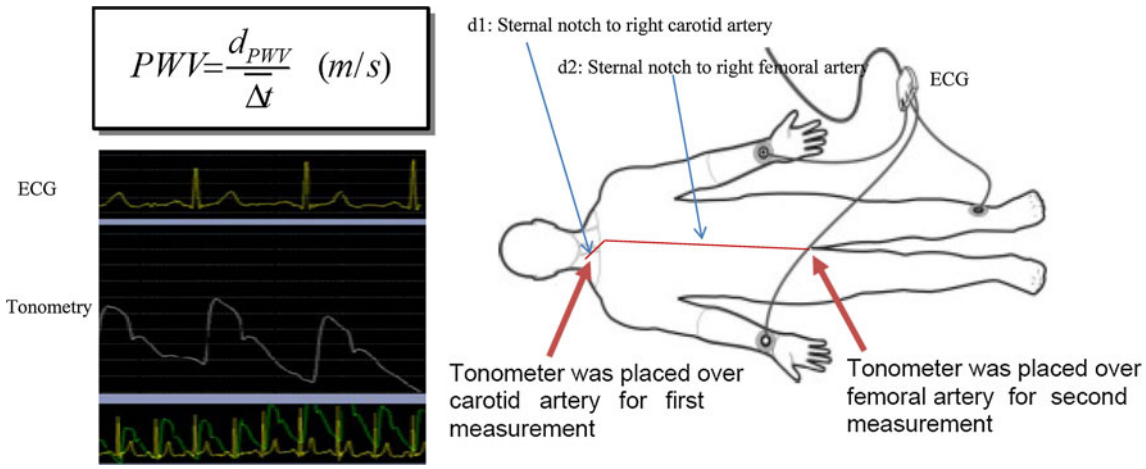

Fig. 1 Measurement of carotid and femoral pulse wave velocity using arterial tonometry. Straight distances from strongest point of pulses in the carotid and femoral area to sternal notch were measured. Measured distance (d2–d1) was divided by the transit time and the result was expressed as meters/second

frame of a suitable longitudinal image, with the image magnified to achieve a higher resolution of detail. The CIMT measurement was obtained from four contiguous sites at 1-mm intervals on each carotid artery, and the average of all eight measurements was used for analysis. All measurements were performed by the same radiologist who was blinded to patient data. The intra-observer mean absolute difference in measuring the common carotid intima–media thickness was 0.026 ± 0.043 mm (coefficient of variation, 1.6 %; intra-class correlation, 0.95).

Biochemical Measurements

Blood samples were drawn by venipuncture to evaluate routine blood parameters after fasting for at least 8 h. Fasting blood glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride levels were recorded. Glucose and lipid profile were determined by standard methods. Serum CRP was analyzed using a nephelometric technique (Beckman Coulter Immage 800; Fullerton, CA, USA; normal range 0–0.8 mg/dl).

Statistical Analysis

Continuous variables were given as mean ± SD; categorical variables were defined as percentage. Data were tested for normal distribution using the Kolmogorov–Smirnov test. The student's t test was used for the univariate analysis of continuous numerical variables, and the χ^2-test for the categorical variables. Mean values were compared by ANOVA among different groups. Linear regression analysis including variables that were significantly different in univariate analysis was performed to investigate the independent predictors for PWV and CIMT. All tests of significance were two-tailed. Statistical significance was defined as $p < 0.05$. The SPSS statistical software (SPSS for Windows, version 15.0, Inc.; Chicago, IL, USA) was used for all statistical calculations.

Results

Patient Characteristics and UC Activity

Among patients with UC, two had (5 %) extensive colitis, five had (14 %) left-sided colitis, 18 had (49 %) distal colitis and 12 had (32 %) rectitis. There was not any extraintestinal manifestation and history of complication as fistulas, stricture and abscess. All patients had active disease at admission, two (5 %) were severe, nine (25 %) moderate and 26 (70 %) with mild disease. Patients were treated with aminosalicylates at admission. Four (11 %) patients required corticosteroids and immunosuppressive agents during treatment. Biologic agents such as infliximab were added to the treatment regimen in two patients (5 %) with extensive colitis.

Clinical Characteristics

The characteristics of the patients are presented in Table 1. UC patients were middle aged (48 ± 15) and predominantly male (57 %). Clinical parameters were similar between patients with UC and control subjects except for male preponderance (57 % vs. 30 %, $p = 0.029$) in patients with UC.

Biochemical Measurements

Erythrocyte sedimentation rate (22.4 ± 18.4 vs. 13.5 ± 7.3 mm/h, $p = 0.022$), CRP (0.83 ± 1.19 vs. 0.34 ± 0.24 mg/dl, $p = 0.041$), and creatinine concentrations

Table 1 Demographic and clinical characteristics of study participants

Parameters	UC group ($N = 37$)	Control group ($N = 30$)	p value[a]
Age (years)	48 ± 15	45 ± 8	NS
Gender (male, %)	57 %	30 %	0.029
BMI (kg/m^2)	27.0 ± 4.4	27.5 ± 4.1	NS
Hypertension	16 %	13 %	NS
Diabetes mellitus	5 %	7 %	NS
Smoking (%)	16 %	13 %	NS
Total cholesterol (mg/dl)	196 ± 38	198 ± 46	NS
Triglycerides (mg/dl)	135 ± 66	135 ± 83	NS
HDL cholesterol (mg/dl)	45 ± 11	45 ± 9	NS
LDL cholesterol (mg/dl)	135 ± 39	126 ± 36	NS
Creatinine (mg/dl)	0.81 ± 0.18	0.70 ± 0.14	0.015
Glucose (mg/dl)	104 ± 18	102 ± 16	NS
Hemoglobin (mg/dl)	13.6 ± 1.8	13.4 ± 1.7	NS
Leukocytes (10^3 mm^{-3})	7.74 ± 2.38	7.37 ± 1.59	NS
Platelets (10^3 mm^{-3})	309 ± 72	278 ± 65	NS
CRP (mg/dl)	0.83 ± 1.19	0.34 ± 0.24	0.041
ESR (mm/h)	22.4 ± 18.4	13.5 ± 7.3	0.022
CIMT (mm)	0.86 ± 0.15	0.55 ± 0.29	<0.001
CF-PWV (m/s)	8.94 ± 2.98	7.17 ± 1.73	0.004
Disease characteristics			
Truelove and Witts classification			
Mild (n, %)	26, 70 %	–	–
Moderate (n, %)	9, 25 %	–	–
Severe (n, %)	2, 5 %	–	–
Localization of disease involvement		–	–
Extensive (n, %)	2, 5 %	–	–
Left side (n, %)	5, 14 %	–	–
Distal (n, %)	18, 49 %	–	–
Rectitis (n, %)	12, 32 %	–	–
Medications			
Aminosalicylates	37, 100 %	–	–
+Corticosteroid or immunosuppressive (n, %)	4, 11 %	–	–
+Infliximab (n, %)	2, 5 %	–	–

UC ulcerative colitis, *BMI* body mass index, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *CF-PWV* carotid-femoral pulse wave velocity, *CIMT* carotid intima-media thickness, *ESR* erythrocyte sedimentation rate, *CRP* C reactive protein

[a] Student's t test was used for the univariate analysis of continuous numerical variables, and the χ^2-test for categorical variables

(0.81 ± 0.18 vs. 0.70 ± 0.14 mg/dl, $p = 0.015$) were significantly higher in the UC group compared to controls. The remaining laboratory values did not differ between the two groups. There was not any statistically significant correlation between erythrocyte sedimentation rate, CRP, and vascular parameters (data not shown).

UC, PWV, and CIMT

We demonstrated significantly increased cf-PWV (8.94 ± 2.98 vs. 7.17 ± 1.73 m/s, $p = 0.004$) and CIMT (0.86 ± 0.15 vs. 0.55 ± 0.29 mm, $p < 0.001$) in patients with UC. Moreover, when we stratified patients according to disease activity, we revealed prominently increased cf-PWV and CIMT in patients with moderate and severe UC (Table 2). We also analyzed our data in order to demonstrate the relationship between disease localizations and vascular parameters. We found pronounced increments in CIMT and PWV in patients with extensive and left-sided colitis (Table 2).

Multivariate Analyses

We performed linear regression analyses including age, male gender, CRP, and creatinine in order to find

independent predictors of CIMT and PWV. Although linear regression analyses identified UC as an independent predictor of CIMT ($\beta \pm$ SE, 0.39 $\pm$ 0.08; $p < 0.001$), only age independently predicted cf-PWV ($\beta \pm$ SE, 0.08 $\pm$ 0.03; $p = 0.003$) in our study population (Table 3).

Discussion

We documented increased PWV and CIMT together in patients with UC. Our study group included middle-aged patients with a relatively low risk profile. Even though we excluded patients with known cardiovascular disease, according to our study results, patients with UC appear to have higher cardiovascular risk and atherosclerotic burden as determined by vascular tests. Moreover, we revealed higher CIMT and PWV values in patients with higher disease activity and more extensive involvement, compared to patients with mild activity and limited disease.

IBD is a chronic, multisystem disorder which may also have extraintestinal manifestations [16]. Patients with IBD have an increased risk of thromboembolic disease. Even though arterial thromboembolic events including stroke and myocardial infarction are rare in IBD compared to venous thromboembolism, a retrospective cohort analysis demonstrated an increased risk of stroke and myocardial infarction in women aged 40–59. Interestingly, men with IBD did not have an increased risk for arterial thromboembolism [17]. Moreover, even though an association between ischemic heart disease and IBD has been documented [18, 19], an increased cardiovascular mortality has not been observed in patients with IBD [20].

The etiopathogenesis of UC is still not clarified. Even though immune dysregulation resulting in intestinal injury still predominates; data suggests that vascular involvement including microvascular dysfunction with impaired vasodilatory capacity, and increased adhesion molecule expression at microvascular levels may have a role as well [21, 22]. Apart from having the same initial step as endothelial dysfunction and inflammation in pathogenesis, both IBD and atherosclerosis share another potential mediator, CD40/CD40 Ligand (CD40L) dyad. Danese et al. demonstrated that platelets express CD40L in patients with IBD and thus induce microthrombosis and inflammatory response in intestinal microvasculature [23]. However, CD40/CD40L dyad has recently been linked to vascular diseases due to evidence of increased inflammation, thrombosis and atherosclerosis [24]. Previous studies reported an association between arterial stiffness, carotid atherosclerosis and systemic inflammatory disorders such

Table 3 The independent effect of ulcerative colitis on carotid-intima media thickness and carotid-femoral pulse wave velocity

Variables	$\beta \pm$ SE	Beta	p value[a]
CIMT (dependent variable)			
Age (years)	0.01 $\pm$ 0.003	0.289	0.028
Gender (male)	−0.154 $\pm$ 0.107	−0.274	0.158
CRP (mg/dl)	−0.03 $\pm$ 0.04	−0.101	0.436
Creatinine (mg/dl)	−0.03 $\pm$ 0.3	−0.02	0.928
UC (+)	0.39 $\pm$ 0.08	0.705	<0.001
Constant	0.30 $\pm$ 0.21	–	0.163
R^2	0.468		
Cf-PWV (dependent variable)			
Age (years)	0.08 $\pm$ 0.03	0.419	0.003
Gender (male)	−0.9 $\pm$ 0.8	−0.198	0.244
CRP (mg/dl)	−0.12 $\pm$ 0.35	−0.045	0.743
Creatinine (mg/dl)	0.96 $\pm$ 2.3	0.070	0.686
UC (+)	1.19 $\pm$ 0.63	0.259	0.065
Constant	2.98 $\pm$ 1.75	–	0.093
R^2	0.247		

UC ulcerative colitis, *CIMT* carotid intima-media thickness, *CRP* C reactive protein

[a] Linear regression analysis, including variables that were significantly different in univariate analysis, was performed to investigate the independent predictors for CIMT and cf-PWV

Table 2 The values of cf-PWV and CIMT in groups determined by activity and extent of UC

UC activity	Control	Mild	Moderate	Severe	p value[a]
Truelove and Witts classification					
CF-PWV (m/s)	7.17 $\pm$ 1.74	7.58 $\pm$ 1.70	11.7 $\pm$ 3.09	14.0 $\pm$ 1.13	<0.001
CIMT (mm)	0.55 $\pm$ 0.29	0.83 $\pm$ 0.17	0.92 $\pm$ 0.11	0.90 $\pm$ 0.16	<0.001

Localization of IBD	Control	Rectitis	Distal	Left side	Extensive	p value
Localization of disease involvement						
CF-PWV (m/s)	7.17 $\pm$ 1.74	6.54 $\pm$ 1.48	8.94 $\pm$ 1.84	12.1 $\pm$ 3.12	15.2 $\pm$ 0.49	<0.001
CIMT (mm)	0.55 $\pm$ 0.29	0.79 $\pm$ 0.14	0.87 $\pm$ 0.15	0.92 $\pm$ 0.11	1.00 $\pm$ 0.14	<0.001

UC ulcerative colitis, *CF-PWV* carotid-femoral pulse wave velocity, *CIMT* carotid intima-media thickness, *IBD* inflammatory bowel disease

[a] Mean values were compared by ANOVA among different groups

as systemic lupus erythematosus and rheumatoid arthritis [2, 3]. Moreover, impaired flow mediated dilation has also been documented in systemic inflammatory disorders [25, 26]. Therefore, chronic low-grade inflammation might be the cause of increased atherosclerotic burden and vascular aging in patients with UC.

A few studies investigated the effect of IBD on CIMT so far. Papa et al. demonstrated increased CIMT predominantly in patients with UC [27]. Moreover, patients receiving infliximab, an anti-tumor necrosis factor-α antibody, did have similar CIMT values compared to controls. Additionally, Aloi et al. reported increased CIMT and impaired flow mediated dilation (FMD) in pediatric IBD [28]. Conversely, two recent studies found no difference in CIMT in the IBD population [12, 14]. However, several studies, including those with negative results in CIMT, demonstrated impaired flow mediated dilation of brachial artery as the sign of endothelial dysfunction, the initiator of atherosclerosis pathogenesis [14, 29, 30]. Therefore we think that patients with IBD have early atherosclerosis with higher cardiovascular risk, either by common pathogenetic processes including inflammation and CD40/CD40L dyad, or currently unknown factors. This early atherosclerotic burden might be the reason for increased cardiovascular events in the IBD population [19].

We demonstrated more severe impairment in arterial stiffness and higher carotid atherosclerotic burden in patients with extensive and active disease. These correlations might be due to higher levels of immune reactions. Intriguingly, even though CRP and erythrocyte sedimentation rates (ESR) were higher, they were not related to vascular tests; these parameters may only be innocent bystanders. However, since UC is characterized with exacerbations and remissions, single measurement of inflammatory activity may not be adequate to give information regarding the generalized activity of disease. Since we do not have data regarding disease duration, the correlation of these vascular parameters with disease duration would have been revealing. Moreover, only a minority of our patients were on immunosuppressive agents or infliximab. Infliximab treatment not only reduces inflammatory activity but also improves endothelial function in patients with rheumatoid arthritis [31]. We think that chronic low-grade inflammation and bouts of higher inflammatory activity during exacerbations might be the cause of accelerated atherosclerosis and vascular aging in the patient population; however, in the course of UC, the active immune system cells themselves may cause vascular involvement rather than CRP and ESR.

Arterial stiffness, one of the earliest manifestations of adverse structural and functional changes within the arterial wall, is mainly associated with aging and hypertension [32]. Pulse wave velocity, the gold-standard measure of arterial stiffness, has been shown to be an independent predictor of mortality and stroke in the general population [5] and those with end stage renal disease [33], hypertension [34], or diabetes [35]. PWV is significantly associated with the markers of subclinical target organ damage in the coronary, peripheral arterial, and cerebral vascular beds [36]. Therefore, PWV may be considered to be a test of target organ damage in hypertensive patients according to European guidelines on cardiovascular disease prevention [37]. Carotid intima-media thickness, the surrogate of cardiovascular disease, is associated with conventional cardiovascular risk factors and atherosclerosis [9]. Moreover, CIMT relates to several CVD risk scores in the elderly, predicts cardiovascular events, and gives information beyond conventional risk factors [10, 38, 39].

PWV and CIMT are two overlapping processes of aging, with evidence of association [38]. However, Zureik et al. documented an association between PWV and carotid plaques (CIMT $>$ 1.0 mm), while no relationship was found in moderately increased CIMT [40]. These results might lead to the conclusion that arterial stiffness becomes impaired in the later stages of atherosclerosis. Therefore, this information might justify the observed independent relationship between UC and CIMT, whereas the link with PWV was weaker, in our study.

Limitations

Our study has several limitations; the most important is the small sample size. Additional inflammatory biomarkers besides CRP may have been studied. Moreover, our study is cross-sectional in nature; therefore, our results cannot implicate causality. Additionally, patient and control groups significantly differ with respect to gender, which is a predictor of CIMT. Although we corrected for gender in analysis, small sample size might have affected our results. However, in order to decrease variability in measuring atherosclerotic parameters, we utilized validated endpoints, which are the stronger aspects of our study.

Conclusion

We documented increased CIMT and PWV, as validated surrogates of atherosclerosis and arterial stiffness, in patients with UC. Our results support accelerated atherosclerosis and vascular aging with higher cardiovascular risk in patients with UC, either by common pathogenesis or by inflammation. Further studies are required to clarify this issue.

Conflict of interest None.

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